A CASE HIGHLIGHT:

A Patient With Unresectable KIT+ GIST

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CASE OVERVIEW

- 53-year-old woman with epigastric pain and melana diagnosed with c-KIT+ GIST in the stomach
- Endoscopic ultrasound (EUS) suggested invasion of the spleen precluding tumor resection
- Patient was treated with Gleevec 400 mg/d; after 3 months the melana had resolved and a repeat CT showed that the mass decreased in size
- Summary: This patient with unresectable KIT+ GIST responded to Gleevec after 3 months of therapy; response time may vary between 3 and 98 weeks (median 12 weeks), thus oncologists should monitor response over time to assess efficacy and tolerability prior to switching to second-line therapy

PRESENTATION

A 53-year-old woman presented with a history of epigastric pain. An esophagogastroduodenoscopy (EGD) showed signs of gastritis, but was otherwise unremarkable. She was treated for gastritis. However, her abdominal pain persisted and 4 months later she developed melana. Repeat EGD showed a large mass in the stomach. Her hemoglobin was 6.6 g/dL, but her serum comprehensive chemistry panel was otherwise unremarkable. After blood transfusion, her hemoglobin increased to 10 g/dL. The patient had no other medical problems and her ECOG status was 1.

DIAGNOSIS

Considering the patient's gastric symptoms and the mass identified with EGD, what is the appropriate next step in the diagnostic procedure?

The diagnosis and treatment of gastrointestinal stromal tumors (GISTs) should be approached in a multidisciplinary manner, especially when there is a suspicion of GIST. Careful consultation among the primary care physician, gastroenterologist, radiologist, pathologist, and oncologist is important for accurate diagnosis.

The size and nature of the mass, the extent of local invasion, and tumor pathology must first be determined. An important first step is a computed tomography (CT) scan, which may yield information regarding mass size, location, extent of local invasion, and resectability.[1] Endoscopic ultrasonography (EUS), which may accurately distinguish intramural from extramural lesions and determine the size and layer of origin of intramural lesions, is equally important.[2] Because EUS is not available in every institution, it may not be necessary if tumor resectability is clear. Abdominal magnetic resonance imaging may also be useful for determining resectability in certain circumstances.[1] Positron emission tomography (PET) scans can also be used as a confirmatory procedure.[1] Biopsies should be obtained at the time of EUS. Because there are many neoplasms that could be in the intraluminal or abdominal cavity that may not necessarily be GIST,[2] biopsy immunohistochemistry, in particular staining for c-KIT (CD117), is important for making a definitive diagnosis of KIT+ GIST; approximately 95% of GISTs stain positively for c-KIT.[3]

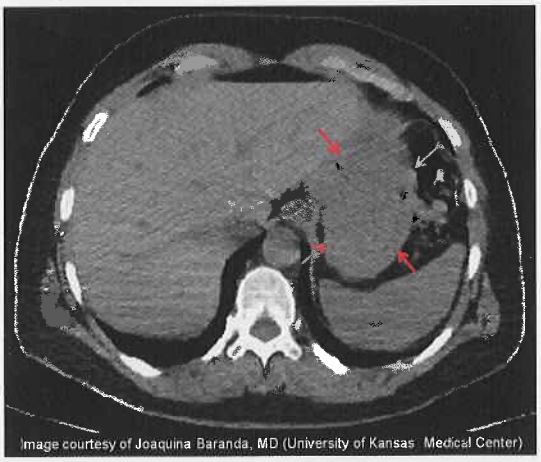

Figure 1: Pre-treatment CT scan

Current Case Diagnosis: A CT scan of the abdomen and pelvis showed a large mass in the cardia and fundus of the stomach (7.0 x 5.6 cm) (Figure 1). EUS showed a lack of fat plane between the mass and the spleen, and a biopsy analysis confirmed that the mass was a c-KIT–positive GIST with a mitotic rate of 10 mitotic figures per 50 high-powered fields (HPF). PET scan showed a large heterogeneous globular soft tissue density in the stomach, confirming the findings by CT. In this patient, the absence of a fat plane between the mass and the spleen suggested invasion of the spleen precluding tumor resection.

TREATMENT AND SAFETY CONSIDERATIONS

Given that the mass is currently unresectable, what is an appropriate treatment option in this case?

Gleevec® (imatinib mesylate) tablets are indicated for patients with KIT–positive unresectable or metastatic malignant GIST.[4] A starting dose of 400 mg/d is recommended; this dose has resulted in an overall response rate in over half of patients with unresectable or metastatic malignant KIT+ GIST (Figure 2).[4] Gleevec 400 mg/d can be continued if a response is obtained or if there are no signs or symptoms of progression in the absence of serious adverse events.

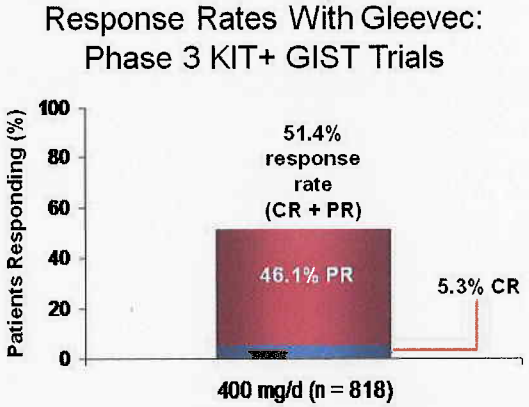

Figure 2: Over half of patients with KIT+ GIST respond to Gleevec

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sician based on the circumstances involved.

Table 1: Serious Adverse Reactions to Gleevec

Fluid retention and edema
Patients should be weighed and monitored regularly for signs and symptoms of edema or serious fluid retention. Severe fluid retention was reported in 9% to 13.1% of patients with KIT+ GIST.

Hemorrhage
In Phase 3 unresectable or metastatic GIST studies, 12.9% of patients reported NCI Grades 3/4 hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients reported severe gastrointestinal (GI) and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Severe congestive heart failure and left ventricular dysfunction
Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully. Patients with signs or symptoms should be evaluated and treated.

Hepatotoxicity
Dose adjustments may be necessary due to hepatotoxicity. Monitoring of hepatic function is recommended.

Hematologic toxicity
Cytopenias, including anemia, neutropenia, and thrombocytopenia, have been reported. Complete blood counts should be performed as indicated.

Gastrointestinal disorders
Gleevec should be taken with food and a large glass of water to minimize possible GI irritation. There have been rare reports, including fatalities, of GI perforation.

Hypereosinophilic cardiac toxicity
In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of Gleevec. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporary withholding of Gleevec.

Dermatologic toxicities
Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported.

Hypothyroidism
Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Gleevec. TSH levels should be closely monitored.

Toxicities from long-term use
Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression.

Pregnancy
Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants.

Safety considerations should be discussed with the patient before initiating therapy and patients need to be carefully monitored over the course of treatment. Patients taking Gleevec may experience serious adverse events (AEs) (Table 1); some serious AEs, such as hepatotoxicity and hematologic toxicities, may require dose adjustment, interruption, or drug discontinuation.[4] The most commonly reported AEs, occurring in over 30% of patients, include edema, fatigue, malaise, lethargy, asthenia, nausea, abdominal pain, cramping, diarrhea, rash, vomiting, myalgia, anemia, and anorexia (Table 2).[4] **For a complete description of adverse events, please see the Important Safety Information on the back cover and the full Gleevec Prescribing Information.**

Table 2: Frequency of Most Common Adverse Reactions with Gleevec*

	400 mg/d n=818	800 mg/d n=822
Edema	77%	86%
Fatigue/malaise/lethargy/asthenia	69%	75%
Nausea	58%	65%
Abdominal pain/cramping	57%	55%
Diarrhea	56%	58%
Rash/desquamation	38%	50%
Vomiting	37%	41%
Myalgia	32%	30%
Anemia	32%	35%
Anorexia	31%	36%
Other GI toxicity	25%	28%
Headache	22%	20%
Other pain (excluding tumor related pain)	20%	21%
Other dermatology/skin toxicity	18%	20%
Leukopenia	17%	20%

*Patients with adverse reactions (all grades) where frequency was ≥20% in any one group (full analysis set) in the Phase 3 unresectable and/or metastatic malignant KIT+ GIST clinical trials.

Current Case Treatment and Outcome: Gleevec 400 mg/d was given for 3 months. Following treatment, the patient's melana resolved and hemoglobin remained between 9.5 and 10.0 g/dL. Her complete chemistry panel remained unremarkable. A repeat CT of the abdomen showed that the mass decreased in size to 4.8 cm (Figure 3), and biopsy indicated a low mitotic rate (0/50 HPF). The patient exhibited occasional nocturnal muscle cramps, with minimal fatigue, and remained at ECOG status 1. The muscle cramps were addressed by supportive care with calcium and magnesium supplements.[5]

This patient responded well to Gleevec 400 mg/d. If the lesion did not decrease in size after 3 months, what would be an appropriate course of action?

Adequate time is needed in order to fully assess individual response. Response to Gleevec therapy may not occur immediately. In one study, the median response time to Gleevec was 12 weeks with a range of 3 to 98 weeks.[4] Mutational analysis of the GIST KIT gene may help treatment decisions; mutation in exon 11 of the KIT gene is common[6] and may be responsive to Gleevec.[7] Progressive disease may occur in about 13% of patients with unresectable or metastatic GIST treated with Gleevec 400 mg/d.[8,9] Dose escalation to 800 mg/d may be considered in such cases if Gleevec is clinically tolerated and toxicity is acceptable.[4] A randomized, phase 3 study reported that approximately 1 in 3 patients who had progressive disease while being treated with Gleevec 400 mg/d benefited from dose escalation to 800 mg/d.[10] It is important to note that edema and rash/related terms may occur more frequently with 800 mg/day dose of Gleevec.[4]

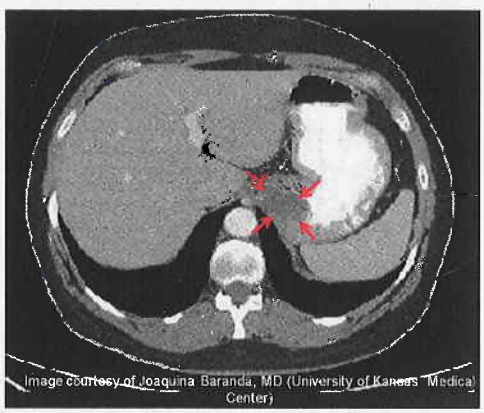

Figure 3: Post-treatment CT scan

SUMMARY

This case describes a patient with an unresectable KIT+ GIST and highlights the importance of using Gleevec (400 mg/d) as front-line therapy for metastatic disease in appropriate patients. Because response time may vary anywhere between 3 to 98 weeks (median 12 weeks), oncologists should monitor response over time to assess efficacy and tolerability before switching to a second-line therapy. In the case of disease progression Gleevec dose escalation from 400 mg/d to 800 mg/d is suggested prior to switching medications in the absence of unacceptable toxicity while advising the patient that edema and rash/related terms may increase with escalation.[4]

REFERENCES

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IMPORTANT SAFETY INFORMATION

- GLEEVEC is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life-threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. If severe fluid retention occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). Dose reduction or treatment interruption may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations)
- Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated
- Hepatotoxicity, occasionally severe, may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- In the Phase 3 unresectable or metastatic GIST studies, 13% of patients reported (NCI Grades 3/4) hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds
- In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of GLEEVEC. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding GLEEVEC
- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression from long-term use
- Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking GLEEVEC tablets and to avoid breast-feeding while taking GLEEVEC tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking GLEEVEC should use adequate contraception. If the patient does become pregnant while taking GLEEVEC, the patient should be advised of the potential hazard to the fetus
- In the Phase 2 unresectable or metastatic GIST trial (400 mg/day; 600 mg/day), severe (NCI Grades 3/4) lab abnormalities—including anemia (3%; 9%) and neutropenia (10%; 11%)—were reported among patients receiving GLEEVEC. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day), severe adverse reactions (NCI Grades 3/4/5), including abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (9%; 8%), vomiting (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), and myalgia (6%; 4%), were reported among patients receiving GLEEVEC
- In the adjuvant treatment of GIST trials (GLEEVEC; placebo), severe (NCI Grades 3 and above) lab abnormalities—increase in liver enzymes (ALT) (3%; 0%), (AST) (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%)—and severe adverse reactions (NCI Grades 3 and above), including abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), nausea (2%; 1%), vomiting (2%; 1%), white blood cell count decreased (1%; 0%), and periorbital edema (1%; 0%), were reported among patients receiving adjuvant treatment with GLEEVEC
- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation

- GLEEVEC is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Significant reductions in imatinib concentrations may occur when GLEEVEC is administered concomitantly with agents that are strong CYP3A4 inducers such as rifampin, St. John's wort, and enzyme-inducing anti-epileptic drugs, eg, phenytoin. The use of concomitant strong CYP3A4 inducers should be avoided. If patients must be administered a strong CYP3A4 inducer, the dosage of GLEEVEC should be increased by at least 50% and clinical response should be carefully monitored. Caution is recommended when GLEEVEC is administered with CYP3A4 inhibitors such as ketoconazole, with CYP2D6 substrates that have a narrow therapeutic window, or with CYP3A4 substrates that have a narrow therapeutic window. Other examples of commonly used drugs that may significantly interact with GLEEVEC include acetaminophen, warfarin, erythromycin, and metoprolol. Grapefruit juice should also be avoided in patients taking GLEEVEC. (Please see full Prescribing Information for other potential drug interactions)
- Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

Common Side Effects of GLEEVEC Tablets

- Almost all patients who received GLEEVEC in the Phase 3 unresectable or metastatic GIST studies experienced adverse reactions at some time. Overall, the incidence of all grades of adverse reactions and the incidence of severe adverse reactions (CTC Grade 3 and above) were similar between the two treatment arms except for edema and rash/related terms, which were reported more frequently in the 800-mg group. The most frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), fatigue (69%; 75%), nausea (58%; 65%), abdominal pain (57%; 55%), diarrhea (56%; 58%), rash and related terms (56%; 70%), vomiting (37%; 41%), myalgia (32%; 30%), anemia (32%; 35%), anorexia (31%; 36%), and arthralgia (14%; 12%). Therapy with GLEEVEC was discontinued for adverse reactions in 5% of patients at both dose levels studied*
- In the adjuvant treatment of GIST trials, almost all GLEEVEC- and placebo-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include (GLEEVEC; placebo) (all Grades) diarrhea (59%; 29%), fatigue (57%; 41%), nausea (53%; 28%), periorbital edema (47%; 15%), decreased hemoglobin (47%; 27%), peripheral edema (27%; 15%), rash (26%; 13%), vomiting (26%; 14%), abdominal pain (21%; 22%), anorexia (17%; 9%), arthralgia (15%; 15%), and myalgia (12%; 12%)*
- In the adjuvant GIST trial, drug was discontinued for adverse events in 17% of GLEEVEC- and 3% of placebo-treated patients. Edema, GI disturbances (nausea, vomiting, abdominal distention, and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation*
- Supportive care may help reduce the severity of some mild-to-moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation
- Patients should be informed to take GLEEVEC exactly as prescribed, and not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

***For more detailed study information, please see full Prescribing Information.**

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A CASE HIGHLIGHT:

Differential Diagnosis and Treatment of Metastatic KIT+ GIST

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CASE OVERVIEW

- 59-year-old woman presented to emergency room with abdominal pain, nausea, and vomiting; CT scan revealed extensive omental, peritoneal, and pelvic nodules, initially suspected to be ovarian carcinoma
- Biopsy revealed uniform, plump spindle cells, positive for c-KIT; surgical assessment deemed the tumors unresectable, and Gleevec was initiated at 400 mg/d
- 5-month follow-up CT showed an ~30%-50% reduction in the tumor size; patient has been on Gleevec for over 3½ years, and remains disease free
- Summary: The case highlights the need for a multidisciplinary collaborative approach for the proper management of patients, and the benefit of Gleevec therapy at 400 mg/d for the treatment of patients with metastatic and/or unresectable KIT+ GIST

NOVARTIS ONCOLOGY

PRESENTATION

A 59-year-old woman presented to the emergency room with abdominal pain, nausea, and vomiting in Fall 2006; she had a history of diabetes mellitus, hypertension, and tuberculosis (treated 9 years prior). A computed tomography (CT) scan in the emergency room revealed extensive omental, peritoneal, and pelvic nodules, some as large as 3.2 cm, associated with cystic necrosis (Figures 1 and 2). Blood work revealed iron deficiency anemia with a low serum iron level of 20 µg/dL, iron saturation of 9%, and a low normal serum ferritin level of 26 ng/mL. Hospital physicians initially suspected that she had ovarian carcinoma.

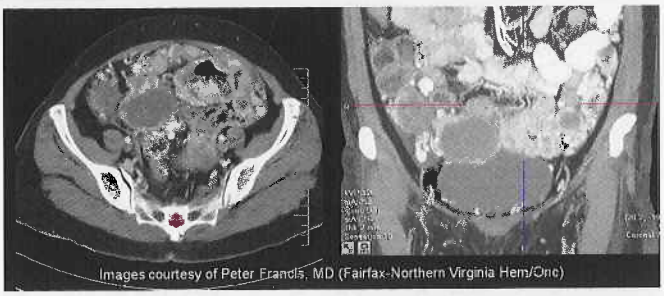

Figure 1: Initial CT scan of pelvic and abdominal masses

DIAGNOSIS

The nodules observed in the pelvic region, omentum, and peritoneum on the CT scan were initially thought to reflect ovarian carcinoma. What might be the next step in the diagnostic procedure?

Clinical symptoms such as abdominal pain, nausea, and vomiting are common to the presentation for several types of abdominal malignancy in women around 60 years of age. Although ovarian cancer is much more common than gastrointestinal stromal tumor (GIST), the differential diagnosis of GIST should be included for any GI or intra-abdominal sarcoma.[1]

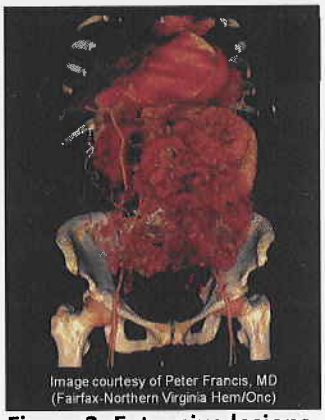

Figure 2: Extensive lesions in the abdomen and pelvis

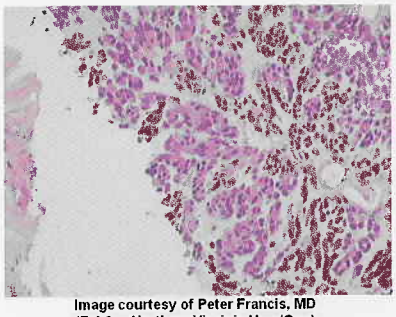

Image courtesy of Peter Francis, MD
(Fairfax-Northern Virginia Hem/Onc)

Figure 3: Spindled-cell type

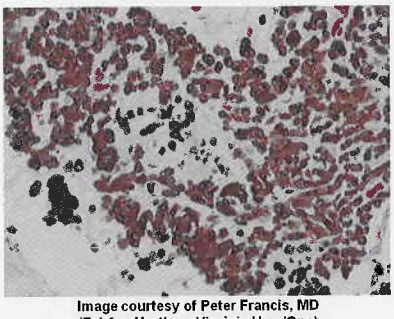

Image courtesy of Peter Francis, MD
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Figure 4: c-KIT staining cells

GISTs are the most common mesenchymal tumor of the GI tract and can occur anywhere along the GI tract, but most commonly in the stomach and small intestine.[2-4] Biopsy of the lesion may be necessary in some patients with a primary GIST.[1] The decision to biopsy may vary from patient to patient and should be based on the extent of the disease, accessibility of the tumor mass, and degree of suspicion for other malignancies.[1] Morphologic analysis and pathology are needed to diagnose a GIST with certainty.[1] Common markers for GIST include c-KIT and CD34; approximately 95% of GISTs express c-KIT (CD117), and about 60%-70% are positive for CD34.[5] Once GIST is suspected, co-management by a multidisciplinary team[1] consisting of a gastroenterologist, pathologist, radiologist, surgeon, and medical oncologist is helpful for ensuring proper diagnosis, treatment selection, and monitoring therapeutic response.

Current Case Diagnosis: The patient underwent an exploratory laparotomy, and biopsies of the mesenteric and omental masses were obtained. At the time of the surgery, the tumors did not appear to be coming from the ovary, contrary to initial assessment. Pathologic analysis of the biopsies revealed a uniform, plump, spindle-cell neoplasm (Figure 3). There was no mitotic activity, and immunohistochemistry revealed that the cells were strongly positive for c-KIT (Figure 4), and CD34. The patient was seen by the surgeon, whereby the KIT+ GISTs were assessed to be inoperable because of the tremendous tumor burden in the abdominal and pelvic cavities.

TREATMENT AND SAFETY CONSIDERATIONS

Pathology results indicated that the tumors were c-KIT+ GISTs. Given the assessment that the metastatic tumors are inoperable, what treatment options are available to the patient?

Gleevec® (imatinib mesylate) tablets are indicated for the treatment of patients with KIT (CD117)-positive unresectable and/or metastatic malignant GIST.[6] In phase 3 trials, more than half of patients with unresectable or metastatic KIT+ GIST

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Hematologic toxicity
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Severe congestive heart failure and left ventricular dysfunction
Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully. Patients with signs or symptoms should be evaluated and treated.

Hepatotoxicity
Dose adjustments may be necessary due to hepatotoxicity. Monitoring of hepatic function is recommended.

Hemorrhage
In Phase 3 unresectable or metastatic GIST studies, 12.9% of patients reported NCI Grades 3/4 hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients reported severe gastrointestinal (GI) and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Gastrointestinal disorders
Gleevec should be taken with food and a large glass of water to minimize possible GI irritation. There have been rare reports, including fatalities, of GI perforation.

Hypereosinophilic cardiac toxicity
In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of Gleevec. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporary withholding of Gleevec.

Dermatologic toxicities
Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported.

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Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression.

Pregnancy
Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants.

Response Rates With Gleevec:
Phase 3 KIT+ GIST Trials

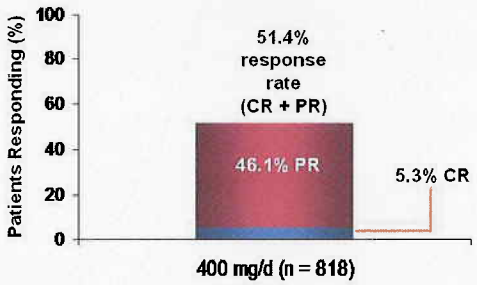

Figure 5: Over half of patients with KIT+ GIST respond to Gleevec

responded to Gleevec 400 mg/d (Figure 5), with a median overall survival of 49 months.[6]

Safety considerations should be discussed with the patient before initiating therapy and patients need to be carefully monitored over the course of treatment. Patients taking Gleevec may experience serious adverse events (AEs) (Table 1); some serious AEs, such as hepatotoxicity and hematologic toxicities, may require dose adjustment, interruption, or drug discontinuation.[6] The most commonly reported AEs, occurring in over 30% of patients, include edema, fatigue, malaise, lethargy, asthenia, nausea, abdominal pain, cramping, diarrhea, rash, vomiting, myalgia, anemia, and anorexia (Table 2).[6] **For a complete description of adverse events, please see the Important Safety Information on the back cover and the full Gleevec Prescribing Information.**

Table 2: Frequency of Most Common Adverse Reactions with Gleevec in the Metastatic Setting*

	400 mg/d n=818	800 mg/d n=822
• Edema	77%	86%
• Fatigue/malaise/lethargy/asthenia	69%	75%
• Nausea	58%	65%
• Abdominal pain/cramping	57%	55%
• Diarrhea	56%	58%
• Rash/desquamation	38%	50%
• Vomiting	37%	41%
• Myalgia	32%	30%
• Anemia	32%	35%
• Anorexia	31%	36%
• Other GI toxicity	25%	28%
• Headache	22%	20%
• Other pain (excluding tumor related pain)	20%	21%
• Other dermatology/skin toxicity	18%	20%
• Leukopenia	17%	20%

*Patients with adverse reactions (all grades) where frequency was ≥20% in any one group (full analysis set) in the Phase 3 unresectable and/or metastatic malignant KIT+ GIST clinical trials.

Current Case Treatment: Gleevec was initiated at 400 mg/d. The only side effect experienced by the patient was mild periorbital edema. An abdominopelvic CT scan 5 months after diagnosis revealed significant improvement, with an estimated 30%-50% reduction in the size of the extensive metastatic tumors.

The patient demonstrated a significant response after 5 months of Gleevec therapy. What are some considerations when deciding whether to continue therapy?

When determining the response to treatment, an important consideration is the median response time to Gleevec therapy, which is 12 weeks with a range of 3 to 98 weeks.[6] Patients should be continuously monitored for disease progression with periodic CT or magnetic resonance imaging (MRI).[1] This patient responded well to Gleevec 400 mg/d. However, if a patient experiences progressive disease with the 400 mg/d dose, a dose increase up to 800 mg/d may be considered, as long as it is clinically tolerated and there are no severe adverse drug reactions.[6] With the exception of edema and rash/related terms, studies have shown that the incidence of AEs in patients with Gleevec at 800 mg/d is the same as those receiving 400 mg/d.[6] One should always assess dose escalation in the context of adverse events; note that dose escalation may not be appropriate for some patients. From the time of initiation of therapy with Gleevec, and throughout stages of treatment for metastatic disease, there should be a continuous dialogue between the physician and the patient on various key issues related to therapy. Patients should be informed regarding expectations for time to response to therapy and the occurrence and proper management of side effects while on Gleevec. Regular conversations about AEs and their management are critical. In the event of progressive metastatic disease, an understanding of associated AEs may affect the decision to dose escalate to Gleevec 800 mg/d.

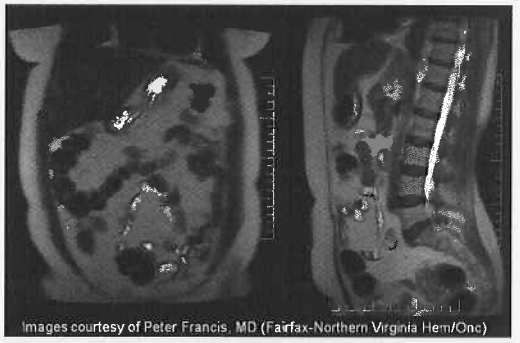

Figure 6: Coronal (left) and sagittal (right) follow-up MRI images

Current Case Outcome: Follow-up MRIs with and without contrast were performed 2 years after the initial diagnosis and showed that the abdomen and pelvis were completely unremarkable (Figures 6 and 7), except for an 8-mm cyst in the right lobe of the liver, which was felt to be unrelated. The patient has been on Gleevec for over 3½ years, and remains free of disease and any supervening medical problems.

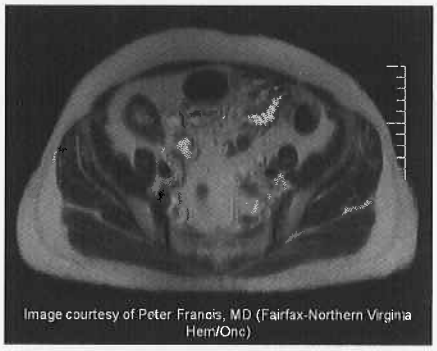

Figure 7: Follow-up pelvic MRI

SUMMARY

This case describes a patient who was initially misdiagnosed as having ovarian carcinoma. The case highlights the need for a multidisciplinary collaborative approach for the proper management of patients, and the benefit of Gleevec therapy at 400 mg/d for the treatment of patients with metastatic and/or unresectable KIT+ GIST.

REFERENCES

1. Referenced with permission from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ Soft Tissue Sarcoma (V.2.2010). Available at: http://www.nccn.org. Accessed April 19, 2010. ©National Comprehensive Cancer Network, Inc. 2010. To view the most recent and complete version of the NCCN Guidelines™, go online to www.nccn.org.
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6. Gleevec® (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Feb 2010.

IMPORTANT SAFETY INFORMATION

- GLEEVEC is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life-threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. If severe fluid retention occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). Dose reduction or treatment interruption may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations)
- Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated
- Hepatotoxicity, occasionally severe, may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- In the Phase 3 unresectable or metastatic GIST studies, 13% of patients reported (NCI Grades 3/4) hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds
- In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of GLEEVEC. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding GLEEVEC
- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression from long-term use
- Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking GLEEVEC tablets and to avoid breast-feeding while taking GLEEVEC tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking GLEEVEC should use adequate contraception. If the patient does become pregnant while taking GLEEVEC, the patient should be advised of the potential hazard to the fetus
- In the Phase 2 unresectable or metastatic GIST trial (400 mg/day; 600 mg/day), severe (NCI Grades 3/4) lab abnormalities—including anemia (3%; 9%) and neutropenia (10%; 11%)—were reported among patients receiving GLEEVEC. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day), severe adverse reactions (NCI Grades 3/4/5), including abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (9%; 8%), vomiting (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), and myalgia (6%; 4%), were reported among patients receiving GLEEVEC
- In the adjuvant treatment of GIST trials (GLEEVEC; placebo), severe (NCI Grades 3 and above) lab abnormalities—increase in liver enzymes (ALT) (3%; 0%), (AST) (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%)—and severe adverse reactions (NCI Grades 3 and above), including abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), nausea (2%; 1%), vomiting (2%; 1%), white blood cell count decreased (1%; 0%), and periorbital edema (1%; 0%), were reported among patients receiving adjuvant treatment with GLEEVEC
- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation

- GLEEVEC is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Significant reductions in imatinib concentrations may occur when GLEEVEC is administered concomitantly with agents that are strong CYP3A4 inducers such as rifampin, St. John's wort, and enzyme-inducing anti-epileptic drugs, eg, phenytoin. The use of concomitant strong CYP3A4 inducers should be avoided. If patients must be administered a strong CYP3A4 inducer, the dosage of GLEEVEC should be increased by at least 50% and clinical response should be carefully monitored. Caution is recommended when GLEEVEC is administered with CYP3A4 inhibitors such as ketoconazole, with CYP2D6 substrates that have a narrow therapeutic window, or with CYP3A4 substrates that have a narrow therapeutic window. Other examples of commonly used drugs that may significantly interact with GLEEVEC include acetaminophen, warfarin, erythromycin, and metoprolol. Grapefruit juice should also be avoided in patients taking GLEEVEC. (Please see full Prescribing Information for other potential drug interactions)
- Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

Common Side Effects of GLEEVEC Tablets

- Almost all patients who received GLEEVEC in the Phase 3 unresectable or metastatic GIST studies experienced adverse reactions at some time. Overall, the incidence of all grades of adverse reactions and the incidence of severe adverse reactions (CTC Grade 3 and above) were similar between the two treatment arms except for edema and rash/related terms, which were reported more frequently in the 800-mg group. The most frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), fatigue (69%; 75%), nausea (58%; 65%), abdominal pain (57%; 55%), diarrhea (56%; 58%), rash and related terms (56%; 70%), vomiting (37%; 41%), myalgia (32%; 30%), anemia (32%; 35%), anorexia (31%; 36%), and arthralgia (14%; 12%). Therapy with GLEEVEC was discontinued for adverse reactions in 5% of patients at both dose levels studied*
- In the adjuvant treatment of GIST trials, almost all GLEEVEC- and placebo-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include (GLEEVEC; placebo) (all Grades) diarrhea (59%; 29%), fatigue (57%; 41%), nausea (53%; 28%), periorbital edema (47%; 15%), decreased hemoglobin (47%; 27%), peripheral edema (27%; 15%), rash (26%; 13%), vomiting (26%; 14%), abdominal pain (21%; 22%), anorexia (17%; 9%), arthralgia (15%; 15%), and myalgia (12%; 12%)*
- In the adjuvant GIST trial, drug was discontinued for adverse events in 17% of GLEEVEC- and 3% of placebo-treated patients. Edema, GI disturbances (nausea, vomiting, abdominal distention, and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation*
- Supportive care may help reduce the severity of some mild-to-moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation
- Patients should be informed to take GLEEVEC exactly as prescribed, and not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

***For more detailed study information, please see full Prescribing Information.**

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A CASE HIGHLIGHT:

Management of a Progressive Metastatic KIT+ GIST

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CASE OVERVIEW

- 75-year-old man presented to his PCP because he felt an abdominal mass; a gastric lesion was resected and diagnosed postoperatively as a GIST.
- Three years later, the patient returned with abdominal pain, nausea, and vomiting; KIT+ GIST metastases were present in his liver, and the patient was initiated on Gleevec 400 mg/d.
- Following 5 years of Gleevec therapy, disease progression was observed; Gleevec dose was increased to 800 mg/d, and the disease is now stable. In clinical trials, the frequency of adverse reactions was similar between 400 mg/d and 800 mg/d, with the exception of edema and rash/related terms, which occurred more frequently in the 800 mg/d arm.
- Summary: This case highlights the benefit of treating unresectable, metastatic KIT+ lesions with Gleevec therapy at 400 mg/d, the importance of dose escalation to 800 mg/d in the case of disease progression, and the management of adverse events.

NOVARTIS ONCOLOGY

PRESENTATION

In the summer of 2000, a 75-year-old male without any significant medical history presented to his primary care physician because he felt an abdominal mass. Initial workup included an endoscopy, which revealed a large lesion suggestive of a gastric gastrointestinal stromal tumor (GIST).

DIAGNOSIS

Considering the patient's symptoms and findings by endoscopy, what might be the next appropriate step?

Patients diagnosed with GIST are best managed in a multidisciplinary setting[1] by a team of gastroenterologists, pathologists, radiologists, surgeons, and medical oncologists that has previous experience in diagnosing and treating GIST.

The initial workup should include computed tomography (CT) scans, an endoscopy, and, possibly, positron emission tomography scans.[1] An experienced endoscopist should perform an endoscopy and decide whether or not it is safe to biopsy the tumor. These tumors are often fragile, and bleeding complications have been known to arise after biopsying GISTs.[1] In many cases, biopsy can be eliminated in favor of surgical resection and pathological workup after the specimen has been resected. A surgeon should be involved in determining if the tumor is resectable, as surgery remains the mainstay of treatment for patients with resectable GISTs that are 2 cm or larger, and without significant risk of morbidity.[1] For most resectable tumors, pathology assessment is critical to confirm the diagnosis and help with appropriate treatment planning.[2]

Current Case Diagnosis: The patient underwent a partial gastrectomy, and the pathology report indicated the tumor was a GIST. At the time the patient presented in 2000, c-KIT (CD117) expression was not routinely tested for, as it is now, in diagnosing a GIST. Three years later, the patient returned to his primary care physician with complaints of abdominal pain, nausea, and vomiting. A CT scan was performed and revealed a 7-cm area of heterogeneity with decreased attenuation in the posterior aspect of the right lobe of the liver and a second lesion in the left lobe of the liver (Figure 1).

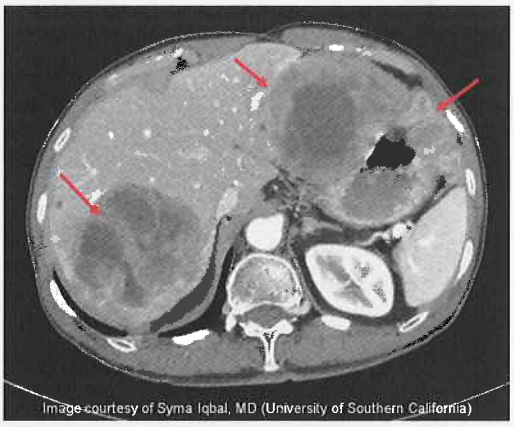

Figure 1: CT of liver metastases

TREATMENT AND SAFETY CONSIDERATIONS

Considering the patient's history and the mass identified with CT, what is the recommended treatment approach?

Liver metastasis and/or dissemination within the abdominal cavity are the most common clinical manifestations of malignant GIST, although they may metastasize to other locations as well.[3,4] Given the patient's history, the observed lesion on the CT scan is most likely a GIST. However, it is important to ensure that the lesion is not from another metastatic process, eg, colon cancer or other common tumors. Currently, immunohistochemical analysis of c-KIT expression is routinely performed to confirm a GIST diagnosis.[1] In the case of this patient, his metastases were confirmed to be c-KIT positive. Gleevec® (imatinib mesylate) tablets are indicated for patients with KIT-positive, unresectable and/or metastatic malignant GIST.[5] For adult patients with metastatic or unresectable KIT+ GIST, the recommended starting dose of Gleevec is 400 mg/d.[5]

Safety considerations should be discussed with the patient before initiating therapy and patients need to be carefully monitored over the course of treatment. Patients taking Gleevec may experience serious adverse events (AEs) (Table 1); some serious AEs, such as hepatotoxicity and hematologic toxicities, may require dose adjustment, interruption, or drug discontinuation.[5] The most commonly reported AEs, occurring in over 30% of patients, include edema, fatigue, malaise, lethargy, asthenia, nausea, abdominal pain, cramping, diarrhea, rash, vomiting, myalgia, anemia, and anorexia (Table 2).[5] **For a complete description of adverse events, please see the Important Safety Information on the back cover and the full Gleevec Prescribing Information.**

ve and may vary by patient. Portions of this presentation are designed for discussion or illustrative
t principles of guidelines in this presentation is not intended to represent the opinion or advice of
sician based on the circumstances involved.

Table 1: Serious Adverse Reactions to Gleevec

Fluid retention and edema
Patients should be weighed and monitored regularly for signs and symptoms of edema or serious fluid retention. Severe fluid retention was reported in 9% to 13.1% of patients with KIT+ GIST.

Hematologic toxicity
Cytopenias, including anemia, neutropenia, and thrombocytopenia, have been reported. Complete blood counts should be performed as indicated.

Severe congestive heart failure and left ventricular dysfunction
Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully. Patients with signs or symptoms should be evaluated and treated.

Hepatotoxicity
Dose adjustments may be necessary due to hepatotoxicity. Monitoring of hepatic function is recommended.

Hemorrhage
In Phase 3 unresectable or metastatic GIST studies, 12.9% of patients reported NCI Grades 3/4 hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients reported severe gastrointestinal (GI) and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Gastrointestinal disorders
Gleevec should be taken with food and a large glass of water to minimize possible GI irritation. There have been rare reports, including fatalities, of GI perforation.

Hypereosinophilic cardiac toxicity
In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of Gleevec. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporary withholding of Gleevec.

Dermatologic toxicities
Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported.

Hypothyroidism
Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Gleevec. TSH levels should be closely monitored.

Toxicities from long-term use
Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression.

Pregnancy
Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants.

Table 2: Frequency of Most Common Adverse Reactions with Gleevec in the Metastatic Setting*

	400 mg/d n=818	800 mg/d n=822
Edema	77%	86%
Fatigue/malaise/lethargy/asthenia	69%	75%
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Other GI toxicity	25%	28%
Headache	22%	20%
Other pain (excluding tumor related pain)	20%	21%
Other dermatology/skin toxicity	18%	20%
Leukopenia	17%	20%

*Patients with adverse reactions (all grades) where frequency was ≥20% in any one group (full analysis set) in the Phase 3 unresectable and/or metastatic malignant KIT+ GIST clinical trials.

Current Case Treatment and Outcome: A CT-guided biopsy was performed, and pathology confirmed spindle cell KIT+ GIST. The patient was initiated on Gleevec 400 mg/d, which was well tolerated. He experienced mild periorbital edema; however, no supportive management was necessary. Six months after starting Gleevec, a CT scan revealed a decrease in the size of the hepatic metastases (Figure 2). Subsequent CT monitoring over several years showed stable disease. After 5 years on Gleevec at 400 mg/d, a restaging CT revealed progressive disease with a new 5.8- by 3.8-cm exocytic left lateral liver mass impressing upon the greater curvature of the stomach (Figure 3).

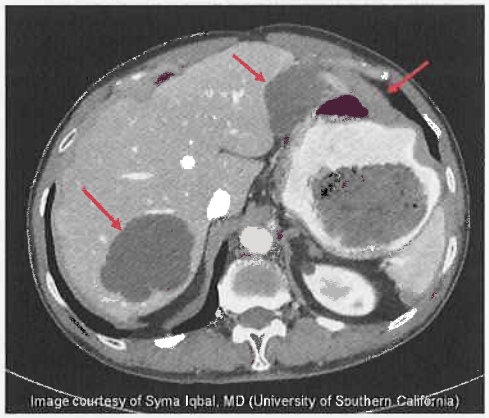

Figure 2: Decrease in tumor size after 6 months of Gleevec

The patient is presenting with signs and symptoms of progressive disease. What would be an appropriate next step in the treatment procedure?

While a majority of patients respond positively to Gleevec, some experience disease progression after either a positive response or stable disease of varying periods of time.[5] If there is evidence of disease progression while the patient is on Gleevec 400 mg/d, increasing the dose to 800 mg/d should be considered.[5] There is potential for experiencing more toxicities or worsening of current toxicities with an increased Gleevec dose. While the incidences of many side effects are similar with the 400- and 800-mg/d doses, edema and rash/related terms may be seen more frequently with 800 mg/d.[5] Renal complications or a renal comorbid state should be carefully monitored. Patients with either renal impairment or hepatic insufficiency may require special considerations.[5] Always assess dose escalation in the context of adverse events; note that dose escalation may not be appropriate for some patients.

Current Case Follow-Up: Gleevec dosage was increased to 800 mg/d. Potential AEs, including increasing edema, the potential for congestive heart failure, hepatotoxicity, hypothyroidism, and more common side effects were discussed with the patient, although the patient had been tolerating 400 mg/d well. The patient did develop mild peripheral edema (grade 1-2) and periorbital edema, which were managed by diuretics. There was no associated shortness of breath or any other significant symptoms. No dose adjustments were required. A CT scan 1 year after dose escalation revealed an unchanged mass, consistent with stable disease (Figure 4). The patient continues to be monitored.

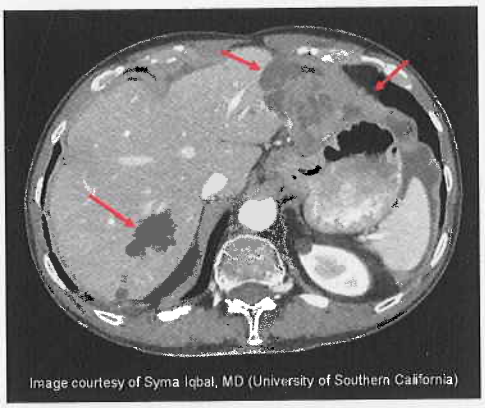

Figure 3: Progression at 5 years

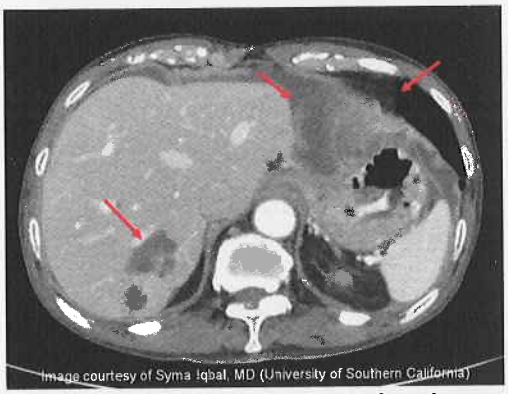

Figure 4: Stable disease 1 year after dose escalation

SUMMARY

This case describes a patient who, following initial resection of a gastric GIST, returned with an advanced KIT+ GIST where resection was not possible. This case highlights the benefit of treating unresectable, metastatic KIT+ lesions with Gleevec therapy at 400 mg/d, the importance of dose escalation to 800 mg/d in the case of disease progression, and the management of adverse events.

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- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression from long-term use
- Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking GLEEVEC tablets and to avoid breast-feeding while taking GLEEVEC tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking GLEEVEC should use adequate contraception. If the patient does become pregnant while taking GLEEVEC, the patient should be advised of the potential hazard to the fetus
- In the Phase 2 unresectable or metastatic GIST trial (400 mg/day; 600 mg/day), severe (NCI Grades 3/4) lab abnormalities—including anemia (3%; 9%) and neutropenia (10%; 11%)—were reported among patients receiving GLEEVEC. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day), severe adverse reactions (NCI Grades 3/4/5), including abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (9%; 8%), vomiting (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), and myalgia (6%; 4%), were reported among patients receiving GLEEVEC
- In the adjuvant treatment of GIST trials (GLEEVEC; placebo), severe (NCI Grades 3 and above) lab abnormalities—increase in liver enzymes (ALT) (3%; 0%), (AST) (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%)—and severe adverse reactions (NCI Grades 3 and above), including abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), nausea (2%; 1%), vomiting (2%; 1%), white blood cell count decreased (1%; 0%), and periorbital edema (1%; 0%), were reported among patients receiving adjuvant treatment with GLEEVEC
- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation

- GLEEVEC is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Significant reductions in imatinib concentrations may occur when GLEEVEC is administered concomitantly with agents that are strong CYP3A4 inducers such as rifampin, St. John's wort, and enzyme-inducing anti-epileptic drugs, eg, phenytoin. The use of concomitant strong CYP3A4 inducers should be avoided. If patients must be administered a strong CYP3A4 inducer, the dosage of GLEEVEC should be increased by at least 50% and clinical response should be carefully monitored. Caution is recommended when GLEEVEC is administered with CYP3A4 inhibitors such as ketoconazole, with CYP2D6 substrates that have a narrow therapeutic window, or with CYP3A4 substrates that have a narrow therapeutic window. Other examples of commonly used drugs that may significantly interact with GLEEVEC include acetaminophen, warfarin, erythromycin, and metoprolol. Grapefruit juice should also be avoided in patients taking GLEEVEC. (Please see full Prescribing Information for other potential drug interactions)
- Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

Common Side Effects of GLEEVEC Tablets

- Almost all patients who received GLEEVEC in the Phase 3 unresectable or metastatic GIST studies experienced adverse reactions at some time. Overall, the incidence of all grades of adverse reactions and the incidence of severe adverse reactions (CTC Grade 3 and above) were similar between the two treatment arms except for edema and rash/related terms, which were reported more frequently in the 800-mg group. The most frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), fatigue (69%; 75%), nausea (58%; 65%), abdominal pain (57%; 55%), diarrhea (56%; 58%), rash and related terms (56%; 70%), vomiting (37%; 41%), myalgia (32%; 30%), anemia (32%; 35%), anorexia (31%; 36%), and arthralgia (14%; 12%). Therapy with GLEEVEC was discontinued for adverse reactions in 5% of patients at both dose levels studied*
- In the adjuvant treatment of GIST trials, almost all GLEEVEC- and placebo-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include (GLEEVEC; placebo) (all Grades) diarrhea (59%; 29%), fatigue (57%; 41%), nausea (53%; 28%), periorbital edema (47%; 15%), decreased hemoglobin (47%; 27%), peripheral edema (27%; 15%), rash (26%; 13%), vomiting (26%; 14%), abdominal pain (21%; 22%), anorexia (17%; 9%), arthralgia (15%; 15%), and myalgia (12%; 12%)*
- In the adjuvant GIST trial, drug was discontinued for adverse events in 17% of GLEEVEC- and 3% of placebo-treated patients. Edema, GI disturbances (nausea, vomiting, abdominal distention, and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation*
- Supportive care may help reduce the severity of some mild-to-moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation
- Patients should be informed to take GLEEVEC exactly as prescribed, and not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

***For more detailed study information, please see full Prescribing Information.**

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